

Amendments to the Claims:

*C14*  
*Clms 1-11 Cancelled*

12. (Currently Amended) A method of treating a subject for a cancer characterized by overexpression of the HER2 receptor protein ~~in a subject~~, said method comprising concurrent therapy with an anti-HER2 antibody or fragment thereof and interleukin-2 (IL-2) or biologically active variant thereof, wherein said concurrent therapy comprises administering to said subject at least one therapeutically effective dose of said IL-2 or variant thereof in combination with a dosing regimen for said anti-HER2 antibody or fragment thereof, wherein said dosing regimen for said anti-HER2 antibody or fragment thereof comprises administering to said subject at least one therapeutically effective dose of said anti-HER2 antibody or fragment thereof, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 1.0 mg/kg to about 10.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.5 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 4.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>; wherein said variant of said IL-2 has at least 70% sequence identity with said IL-2 as calculated using the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4, and wherein said fragment of said anti-HER2 antibody retains the ability of said anti-HER2 antibody to bind the HER2 receptor protein.

13. (Currently Amended) The method of claim 12, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 2.0 mg/kg to about 9.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.6 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 3.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

14. (Currently Amended) The method of claim 13, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 3.0 mg/kg to about 8.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.8 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 1.5 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

15. (Currently Amended) The method of claim 14, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is about ~~4.0 mg/m<sup>2</sup>~~ 4.0 mg/kg and

wherein said therapeutically effective dose of said IL-2 or variant thereof is about 1.0  $\text{mIU/m}^2$   $\text{MIU/m}^2$ .

16. (Currently Amended) A method of treating a subject for a cancer characterized by overexpression of the HER2 receptor protein ~~in a subject~~, said method comprising concurrent therapy with an anti-HER2 antibody or fragment thereof and interleukin-2 (IL-2) or biologically active variant thereof, wherein said concurrent therapy comprises a first administration of a therapeutically effective dose of said IL-2 or variant thereof on day 1 of a treatment period followed by a first administration of a therapeutically effective dose of said anti-HER2 antibody or fragment thereof within 6 days of said first administration of said therapeutically effective dose of said IL-2 or variant thereof to said subject, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 1.0 mg/kg to about 10.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.5  $\text{mIU/m}^2$   $\text{MIU/m}^2$  to about 4.0  $\text{mIU/m}^2$   $\text{MIU/m}^2$ ; wherein said variant of said IL-2 has at least 70% sequence identity with said IL-2 as calculated using the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4, and wherein said fragment of said anti-HER2 antibody retains the ability of said anti-HER2 antibody to bind the HER2 receptor protein.

17. (Currently Amended) A method of treating a subject for a cancer characterized by overexpression of the HER2 receptor protein ~~in a subject~~, said method comprising concurrent therapy with an anti-HER2 antibody or fragment thereof and interleukin-2 (IL-2) or biologically active variant thereof, wherein said concurrent therapy comprises multiple dosing of a therapeutically effective dose of said anti-HER2 antibody or fragment thereof and a therapeutically effective dose of said IL-2 or variant thereof, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 1.0 mg/kg to about 10.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.5  $\text{mIU/m}^2$   $\text{MIU/m}^2$  to about 4.0  $\text{mIU/m}^2$   $\text{MIU/m}^2$ ; wherein said variant of said IL-2 has at least 70% sequence identity with said IL-2 as calculated using the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap

penalty of 4, and wherein said fragment of said anti-HER2 antibody retains the ability of said anti-HER2 antibody to bind the HER2 receptor protein.

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18. (Currently Amended) The method of claim 17, wherein said multiple dosing comprises administering to said subject said therapeutically effective dose of said IL-2 or variant thereof and said therapeutically effective dose of said anti-HER2 antibody or fragment thereof during an introductory cycle, wherein said introductory cycle comprises daily administration of said therapeutically effective dose of said IL-2 or variant thereof on day 1 of said introductory cycle through day 20 of said introductory cycle, and a single administration of said therapeutically effective dose of said anti-HER2 antibody or fragment thereof on day 7 of said introductory cycle.

19. (Currently Amended) The method of claim 18, further comprising administering said therapeutically effective dose of said IL-2 or variant thereof and said therapeutically effective dose of said anti-HER2 antibody or fragment thereof during at least one subsequent cycle, wherein said subsequent cycle comprises daily administration of said therapeutically effective dose of said IL-2 or variant thereof on day 1 of said subsequent cycle through day 14 of said subsequent cycle, and administration of said therapeutically effective dose of said anti-HER2 antibody or fragment thereof on day 1 of said subsequent cycle.

20. (Currently Amended) The method of claim 18, further comprising intermediate-dose IL-2 pulsing on days 8-10 of said introductory cycle, wherein said pulsing comprises administering in place of said therapeutically effective dose of said IL-2 or variant thereof an intermediate dose of ~~a pharmaceutical composition comprising said~~ said IL-2 or variant thereof, wherein said intermediate dose ~~comprises~~ is about  $12.0 \text{ mIU/m}^2$  MIU/m}^2 ~~IL-2 or variant thereof.~~

21. (Currently Amended) The method of claim 19, further comprising intermediate-dose IL-2 pulsing on days 1-3 of said subsequent cycle, wherein said pulsing comprises administering in place of said therapeutically effective dose of said IL-2 or variant thereof an intermediate dose of ~~a pharmaceutical composition comprising~~ said IL-2 or variant thereof, wherein said intermediate dose ~~comprises~~ is about  $12.0 \text{ mIU/m}^2$  MIU/m}^2 ~~IL-2 or variant thereof.~~

22. (Previously presented) The method of claim 12, wherein said IL-2 or variant thereof is administered subcutaneously.

23. (Previously presented) The method of claim 12, wherein said anti-HER2 antibody comprises at least one human constant region.

24. (Currently amended) The method of claim 12, wherein said anti-HER2 antibody is selected from the group consisting of ~~4D5 and 520C9, or fragment thereof~~ a humanized anti-HER2 antibody, a chimeric anti-HER2 antibody, or a human anti-HER2 antibody, and said fragment thereof retains the ability of said humanized, chimeric, or human anti-HER antibody to bind the HER2 receptor protein.

25. (Currently Amended) The method of claim ~~24~~12, wherein said anti-HER2 antibody is ~~4D5 or~~ a humanized, chimeric, or human form of a murine antibody selected from the group consisting of 4D5 and 520C9.

26. (Currently Amended) The method of claim 12, wherein said therapeutically effective dose of said IL-2 or variant thereof is administered as a pharmaceutical composition selected from the group consisting of a ~~stabilized~~ monomeric IL-2 pharmaceutical composition, a multimeric pharmaceutical IL-2 composition, a ~~stabilized~~ lyophilized IL-2 pharmaceutical composition, and a ~~stabilized~~ spray-dried IL-2 pharmaceutical composition.

27. (Currently Amended) The method of claim 26, wherein said IL-2 or variant thereof is recombinantly produced ~~IL-2 having an amino acid sequence for human IL-2 or variant thereof~~ and said IL-2 is human IL-2.

28. (Currently amended) The method of claim 27, wherein said variant ~~thereof has an amino acid sequence having at least about 70% sequence identity to the amino acid sequence for said human IL-2~~ of human IL-2 is des-alanyl-1, serine-125 human interleukin-2.

29. (Currently Amended) The method of claim 28, wherein said anti-HER2 antibody or fragment thereof comprises at least one human constant region.

30. (Currently Amended) The method of claim 28, wherein said anti-HER2 antibody is selected from the group consisting of ~~4D5 and 520C9, or fragment thereof~~ a humanized anti-HER2 antibody, a chimeric anti-HER2 antibody, or a human anti-HER2 antibody, and said fragment thereof retains the ability of said humanized, chimeric, or human anti-HER antibody to bind the HER2 receptor protein.

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31. (Currently Amended) The method of claim ~~30~~28, wherein said anti-HER2 antibody is ~~4D5 or~~ a humanized, chimeric, or human form of a murine antibody selected from the group consisting of 4D5 and 520C9.

32. (Currently Amended) The method of claim 16, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 2.0 mg/kg to about 9.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.6 ~~miu/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 3.0 ~~miu/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

33. (Currently Amended) The method of claim 32, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 3.0 mg/kg to about 8.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.8 ~~miu/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 1.5 ~~miu/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

34. (Currently Amended) The method of claim 33, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is about ~~4.0 mg/m<sup>2</sup>~~ 4.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is about 1.0 ~~miu/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

35. (Currently Amended) The method of claim 17, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 2.0

mg/kg to about 9.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.6 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 3.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

36. (Currently Amended) The method of claim 35, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 3.0 mg/kg to about 8.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.8 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 1.5 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

37. (Currently Amended) The method of claim 36, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is about 4.0 mg/m<sup>2</sup> and wherein said therapeutically effective dose of said IL-2 or variant thereof is about 1.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

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38. (Currently Amended) The method of claim 18, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 2.0 mg/kg to about 9.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.6 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 3.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

39. (Currently Amended) The method of claim 38, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 3.0 mg/kg to about 8.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.8 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 1.5 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

40. (Currently Amended) The method of claim 39, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is about ~~4.0 mg/m<sup>2</sup>~~ 4.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is about 1.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

41. (Currently Amended) The method of claim 19, further comprising intermediate-dose IL-2 pulsing on days 8-10 of said introductory cycle and on days 1-3 of said subsequent cycle, wherein said pulsing comprises administering in place of said therapeutically effective dose of said IL-2 or variant thereof an intermediate dose of ~~a pharmaceutical composition~~

~~comprising said IL-2 or variant thereof, wherein said intermediate dose comprises is about 12.0 mIU/m<sup>2</sup> IL-2 or variant thereof.~~

42. (Currently Amended) A method of treating a subject for a cancer characterized by overexpression of the HER2 receptor protein ~~in a subject~~, said method comprising concurrent therapy with an anti-HER2 antibody or fragment thereof and interleukin-2 (IL-2) or biologically active variant thereof, wherein said concurrent therapy comprises daily administration of a therapeutically effective dose of said IL-2 or variant thereof on day 1 of an introductory cycle through day 20 of said introductory cycle, and a single administration of a therapeutically effective dose of said anti-HER2 antibody or fragment thereof on day 7 of said introductory cycle; wherein said variant of said IL-2 has at least 70% sequence identity with said IL-2 as calculated using the ALIGN program with a PAM 120 weight residue table, a gap length penalty of 12, and a gap penalty of 4, and wherein said fragment of said anti-HER2 antibody retains the ability of said anti-HER2 antibody to bind the HER2 receptor protein.

43. (Currently Amended) The method of claim 42, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 1.0 mg/kg to about 10.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or biologically active variant thereof is in the range from about 0.5 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 4.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

44. (Currently Amended) The method of claim 43, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 2.0 mg/kg to about 9.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.6 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 3.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

45. (Currently Amended) The method of claim 44, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is in the range from about 3.0 mg/kg to about 8.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is in the range from about 0.8 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> to about 1.5 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

46. (Currently Amended) The method of claim 45, wherein said therapeutically effective dose of said anti-HER2 antibody or fragment thereof is about ~~4.0 mg/m<sup>2</sup>~~ 4.0 mg/kg and wherein said therapeutically effective dose of said IL-2 or variant thereof is about 1.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup>.

47. (Currently Amended) The method of claim 42, further comprising administering said therapeutically effective dose of said IL-2 or variant thereof and said therapeutically effective dose of said anti-HER2 antibody or fragment thereof during at least one subsequent cycle, wherein said subsequent cycle comprises daily administration of said therapeutically effective dose of said IL-2 or variant thereof on day 1 of said subsequent cycle through day 14 of said subsequent cycle, and administration of said therapeutically effective dose of said anti-HER2 antibody on day 1 of said subsequent cycle.

48. (Currently Amended) The method of claim 42, further comprising intermediate-dose IL-2 pulsing on days 8-10 of said introductory cycle, wherein said pulsing comprises administering in place of said therapeutically effective dose of said IL-2 or variant thereof an intermediate dose of ~~a pharmaceutical composition comprising~~ said IL-2 or variant thereof, wherein said intermediate dose ~~comprises~~ is about 12.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> ~~IL-2 or variant thereof~~.

49. (Currently Amended) The method of claim 47, further comprising intermediate-dose IL-2 pulsing on days 1-3 of said subsequent cycle, wherein said pulsing comprises administering in place of said therapeutically effective dose of said IL-2 or variant thereof an intermediate dose of ~~a pharmaceutical composition comprising~~ said IL-2 or variant thereof, wherein said intermediate dose ~~comprises~~ is about 12.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> ~~IL-2 or variant thereof~~.

50. (Currently Amended) The method of claim 47, further comprising intermediate-dose IL-2 pulsing on days 8-10 of said introductory cycle and on days 1-3 of said subsequent cycle, wherein said pulsing comprises administering in place of said therapeutically effective dose of said IL-2 or variant thereof an intermediate dose of ~~a pharmaceutical composition comprising~~ said IL-2 or variant thereof, wherein said intermediate dose ~~comprises~~ is about 12.0 ~~mIU/m<sup>2</sup>~~ MIU/m<sup>2</sup> ~~IL-2 or variant thereof~~.



51. (New) The method of claim 12, wherein said cancer is breast cancer.

52. (New) The method of claim 51, wherein said anti-HER2 antibody is a humanized form of a murine antibody selected from the group consisting of 4D5 and 520C9.

53. (New) The method of claim 52, wherein said IL-2 or variant thereof is recombinantly produced, and wherein said IL-2 is human IL-2.

54. (New) The method of claim 16, wherein said cancer is breast cancer.

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56. (New) The method of claim 55, wherein said IL-2 or variant thereof is recombinantly produced, and wherein said IL-2 is human IL-2.

57. (New) The method of claim 17, wherein said cancer is breast cancer.

58. (New) The method of claim 57, wherein said anti-HER2 antibody is a humanized form of a murine antibody selected from the group consisting of 4D5 and 520C9.

59. (New) The method of claim 58, wherein said IL-2 or variant thereof is recombinantly produced, and wherein said IL-2 is human IL-2.

60. (New) The method of claim 42, wherein said cancer is breast cancer.

61. (New) The method of claim 60, wherein said anti-HER2 antibody is a humanized form of a murine antibody selected from the group consisting of 4D5 and 520C9.

C16 62. (New) The method of claim 61, wherein said IL-2 or variant thereof is recombinantly produced, and wherein said IL-2 is human IL-2.

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